



Complete Summary

GUIDELINE TITLE

Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Flemming J, Madarnas Y, Franek J, Breast Cancer Disease Site Group. Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: guideline recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2008 Sep 25. 42 p. (Evidence-based series; no. 1-13). [85 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

- Locally advanced breast cancer
- Metastatic breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if, compared to tamoxifen and aromatase inhibitors, fulvestrant improves outcomes for **first-line** therapy of locally advanced or metastatic breast cancer
- To evaluate if, compared to aromatase inhibitors, fulvestrant improves outcomes for **second-line or later** therapy of locally advanced or metastatic breast cancer
- To evaluate if, compared to therapy alone, fulvestrant in combination with other therapies improves outcomes
- To evaluate the appropriate dose and schedule of fulvestrant
- To evaluate if there are any factors that predict the outcomes of fulvestrant therapy
- To promote evidence-based clinical practice in Ontario, Canada

TARGET POPULATION

Post-menopausal women with locally advanced or metastatic breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Fulvestrant versus tamoxifen, tamoxifen, anastrozole, and exemestane
2. Optimum dose and administration of fulvestrant
3. Combination therapy with fulvestrant plus anastrozole, lapatinib ditosylate – insufficient data for a recommendation
4. Prediction of fulvestrant treatment outcome – insufficient data for a recommendation

MAJOR OUTCOMES CONSIDERED

- Time to progression
- Overall response rate
- Clinical benefit rate
- Duration of response
- Time to treatment failure
- Time to death
- Tolerability
- Quality of life

- Survival rate
- Treatment compliance rate
- Time to steady-state plasma drug levels

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
 Hand-searches of Published Literature (Secondary Sources)
 Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE (January 1996 to June 2008) and EMBASE (January 1996 to April 2008), databases and the Cochrane Central Register of Controlled Trials (CENTRAL) and Systematic Reviews (up to 1st Quarter 2008) were searched in their entirety for the dates indicated. A comprehensive search strategy was used that combined disease-specific (e.g., Breast Neoplasms in MEDLINE or Breast Tumor in EMBASE), treatment-specific (e.g., fulvestrant, Faslodex, or ICI 182,780 [formerly fulvestrant]), and publication-type-specific (e.g. randomized controlled trial) search terms. The combined search strategy, available in Appendix A in the original guideline document, was applied simultaneously to MEDLINE, EMBASE, and CENTRAL and thus included all relevant subject and Emtree headings, text words, and publication types. The Cochrane Library of Systematic Reviews was also searched using simply treatment-specific terms.

On-line conference proceedings from the American Society of Clinical Oncology (ASCO) (<http://www.asco.org/>; up to 2007) and the San Antonio Breast Cancer Symposium (SABCS) (<http://www.sabcs.org/>; up to 2007) were also searched in their entirety for relevant abstracts or presentations using a similar to that identified above. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Ongoing trials were identified through the U.S. National Institute's of Health (NIH) ClinicalTrials.gov and Cancer.gov databases.

All relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were hand searched for additional trials.

Study Selection Criteria

Inclusion Criteria

- Fulvestrant alone or in combination with other systemic agents was evaluated in postmenopausal women with locally advanced or metastatic breast cancer.
- Publication types were randomized Phase II or III trials, clinical practice guidelines, or systematic reviews and/or meta-analyses of randomized trials.
- Locally advanced breast cancers were defined as Stage IIIB or greater.

- Reported outcomes included at least one of the following types of data: time to progression (TTP), time to treatment failure (TTF), objective or complete response rate, progression-free survival, overall survival (OS), compliance/continuation data, and toxicities.
- Clinical trial results were published as peer-reviewed journal articles or publicly available conference abstracts or presentations.

Exclusion Criteria

- Trials that were published in a language other than English, as translation capabilities were not available
- Trials that had not yet reported on evaluable efficacy data and were ongoing at the time of literature searching

NUMBER OF SOURCE DOCUMENTS

Two evidence-based practice guidelines and four relevant Phase III trials were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Methods

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-based Care (CCO's PEBC) use the methods of the Practice Guidelines Development Cycle 1. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one clinician and one methodologist.

Quality Appraisal of Evidence-Based Guidelines

The Appraisal of Guideline Research and Evaluation (AGREE) tool was used by three independent methodologists and one clinician to evaluate the quality of identified evidence-based guidelines. While all scoring domains of the AGREE tool were considered in the evaluation of guidelines, the Rigour of Development domain, describing the rigour of systematic methods in identifying and evaluating

evidence, along with the Overall Rating, were considered to be most relevant in application for this systematic review.

Synthesizing the Evidence

Because of the small number of randomized controlled trials (RCTs) with comparable outcomes, and the fact that two relevant Phase III trials were already evaluated in a combined analysis, no statistical pooling of trial results was conducted.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Breast Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-based Care (CCO's PEBC). The series is a convenient and up-to-date source of the best available evidence on the use of fulvestrant for the treatment of postmenopausal women with locally advanced or metastatic breast cancer developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel and subsequently addressed included:

Issues of multiple reporting: The authors noted that multiple abstract/article publications exist for Trials 0020/0021. An overarching statement about this issue in the section of Literature Search Results and, if/where appropriate, for given trials would be helpful.

Methodological concerns of analyzing trial results for non-inferiority when superiority was expected: In Trials 0020/0021, the Methods sections indicate that the non-inferiority analysis were "not described in the protocol" and were conducted "retrospectively." The DSG has indicated the retrospective nature of these analyses but could take the opportunity to emphasize the limitations of this approach when trials appear to have been originally designed for superiority.

The objective of non-inferiority analyses: From a clinical policy perspective, non-inferiority designs are appropriate when the experimental therapy is hypothesized to have benefits related to secondary outcomes (e.g., quality of life, toxicity, economics, convenience). The experimental therapy may therefore be adopted as a recommended therapy if non-inferiority around major efficacy outcomes is demonstrated (e.g., overall survival, progression-free survival), and a benefit for a secondary outcome is confirmed.

Changes undertaken to address issues raised by Report Approval Panel (January 2008)

Issues of multiple reporting: The authors included a paragraph on concerns regarding multiple reporting in "Section 2: Results" of the original guideline document.

Methodological concerns of analyzing trial results for non-inferiority when superiority was expected: A detailed analysis of methodological concerns and their impact was addressed in "Section 2: Discussion" of the original guideline document. The Breast DSG further provided a consensus statement on how such methodological concerns affect the conclusions and recommendations derived from the evidence in question.

The objective of non-inferiority analyses: Addressed in the point above.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review

Practitioner feedback was obtained through a mailed survey of 113 practitioners in Ontario (56 medical oncologists, 23 radiation oncologists and 34 surgeons). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on January 13, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group (DSG) reviewed the results of the survey.

After reviewing the response rates and comments, the Breast Cancer DSG decided that no further action was required in terms of guideline modification.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

1. *Patients with NO prior endocrine or cytotoxic therapy for advanced disease and NO recent adjuvant therapy (within previous twelve months)*

Fulvestrant is NOT recommended as an alternative to tamoxifen for first-line therapy of locally advanced or metastatic breast cancer in postmenopausal women who have had no prior endocrine or cytotoxic therapy for advanced disease and no recent adjuvant endocrine therapy (within previous twelve months).

2. *Patients who have recurred on prior adjuvant endocrine therapy or have progressed on prior endocrine therapy for advanced disease*

Fulvestrant may be considered as alternative therapy to anastrozole for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (estrogen-receptor-positive [ER+] and/or progesterone-receptor-positive [PgR+]) breast cancer that has recurred on prior adjuvant tamoxifen therapy or progressed on prior tamoxifen therapy for advanced disease. Clinicians should be aware of the methodological concerns of the key evidentiary trials used in formulating this recommendation.

Factors that may influence the choice of fulvestrant versus anastrozole therapy include a slightly decreased, although still significant, incidence of joint disorders and the potential for improved compliance with fulvestrant.

Fulvestrant may be considered as alternative therapy to exemestane for locally advanced or metastatic breast cancer in postmenopausal women with hormone-receptor-positive (ER+ and/or PgR+) breast cancer that has recurred on prior adjuvant nonsteroidal aromatase inhibitor (NSAI) therapy (during or within six months of discontinuation) or progressed on prior NSAI therapy for advanced disease.

Factors that influence the choice of fulvestrant versus exemestane therapy include the potential for improved compliance in favour of fulvestrant.

3. *Recommended dosage*

The recommended dose of fulvestrant for the treatment of locally advanced or metastatic breast cancer is 250 mg intramuscularly (IM) every month OR a loading dose schedule of 500 mg IM day 0, 250 mg IM on days 14 and 28, and 250 mg IM injection every (q) monthly thereafter.

Factors that may influence the choice of a loading dose include a shortened time to reach steady state (within one month vs. three to six months for standard dosage) although this may require further verification.

4. *Combination Fulvestrant*

At present there are no published studies to guide a recommendation regarding the use of fulvestrant in combination with other chemotherapies for first-line or greater treatment of locally advanced or metastatic breast cancer. There are currently two active, ongoing Phase III trials (Southwest Oncology Group [SWOG]-S0226, Functional Assessment of Cancer Therapy [FACT]; see Section 2: Table 5 in the original guideline document) comparing anastrozole vs. anastrozole plus simultaneous fulvestrant for first-line therapy of metastatic breast cancer. In addition, a third, ongoing Phase III trial (Cancer and Leukemia Group B [CALGB]-40302) is examining the use of second-line fulvestrant alone in comparison with the combination of fulvestrant plus lapatinib ditosylate, an epidermal growth factor receptor (EGFR) inhibitor, in human epidermal growth factor receptor 2 (HER2)/*neu*-positive women (see Table 5 in the original guideline document).

5. *Predictive factors of outcome on Fulvestrant therapy*

There is insufficient evidence to guide a definitive recommendation regarding the interpretation of factors to predict an outcome for postmenopausal women undergoing fulvestrant therapy for locally advanced or metastatic breast cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by evidence-based practice guidelines and Phase III trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Effective use of fulvestrant to treat post-menopausal women with advanced breast cancer
- Improved compliance with long-term breast cancer treatment
- Faster achievement of steady state plasma doses of fulvestrant
- Improved quality of life for patients with advanced breast cancer

POTENTIAL HARMS

Side effects of fulvestrant therapy (e.g., hot flashes, joint disorders)

QUALIFYING STATEMENTS

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Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Sep 25

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Breast Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The authors wish to declare no conflicts of interest as of the date of this report.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

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